JACC Vol. 5, No. 1
January 1985:84S–94S

Ultrasonic Assessment of Cardiac Function in the Intact Human Fetus

CHARLES S. KLEINMAN, MD, FACC, RICHARD L. DONNERSTEIN, MD

New Haven, Connecticut

Echocardiography may provide information concerning the structural development of the fetal human heart. The information available from such studies, when interpreted in light of existing knowledge of developmental cardiac physiology, may give insight concerning in utero cardiac pump function. The quantitation of cardiac structural growth in utero has been used to provide growth curves for the chambers of the fetal heart. Disparity in the ratio of right ventricular/left ventricular size (normally 1.0 to 1.2) may suggest acute ventricular failure and dilation. Electromechanical analysis using M-mode techniques may be used to analyze and monitor the treatment of fetal cardiac arrhythmias and provide systolic time interval analysis. Doppler waveform analysis provides information concerning directional flow and vascular impedance and Doppler flowmetry has promise for the measurement of fetal aortic and umbilical venous blood flows. Such studies have increased our understanding of fetal circulatory function and have practical implications for the establishment of fetal cardiac diagnosis and treatment programs.

(J Am Coll Cardiol 1985;5:84S–94S)

Fetal echocardiographic studies utilizing commercially available two-dimensional, M-mode and pulsed Doppler instruments have become an important adjunct to the obstetric evaluation of high risk pregnancies (1–4). Data concerning cardiac structure and rhythm may be gleaned from such studies, with successful imaging attainable between 18 weeks' gestation and term in 90 to 95% of the cases examined.

It is the aim of this report to review the role of fetal echocardiography as a means of assessing cardiac pump function and the status of the fetal circulatory system in the second and third trimester human fetus. We will review the use of volumetric analysis of the fetal heart as well as the timing of electromechanical events as a means of evaluating cardiac performance. We will also review the use of the fetal echocardiogram for the analysis of cardiac rhythm. These data will be interpreted in the context of the existing body of information that has been generated in laboratories utilizing fetal animal models. Finally, the practical application of these principles for the analysis of hydrops fetalis, fetal cardiac arrhythmias and fetal cardiomyopathies will be presented. The indications for and potential problems unique to studies in the intact fetus and the sensitivity and specificity of these techniques will also be addressed.

From the Departments of Pediatrics and Diagnostic Imaging, Yale University School of Medicine, New Haven, Connecticut. This study was supported by a grant from the March of Dimes, White Plains, New York.
Address for reprints: Charles S. Kleinman, MD, Section of Pediatric Cardiology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510.

Quantitative Fetal Echocardiographic Studies

The nature of the subject under study (that is, the intact human fetus) limits our ability to manipulate the subject's environment and, therefore, to control such variables as preload, afterload, heart rate and myocardial inotropic state. It is, therefore, impossible to generate the pressure-volume data that would be necessary to characterize muscle function (5).

M-mode echocardiography affords the advantage of rapid sampling rates and hardcopy representation of cardiac motion against time. However, simultaneous or sequential two-dimensional imaging is necessary to define the examining plane and the level within the heart at which the measurements are obtained. The equipment currently available limits M-mode scanning to planes that are either perpendicular to the skin's surface (linear array scanners) or along selected planes within the "fan" of mechanically or electronically swept sector scanners. If the heart of the fetus cannot be approached in a manner placing the M-mode examining plane perpendicular to the long axis of the heart, the angulated view of the ventricles so obtained may introduce considerable error in ventricular chamber measurement. In addition, the lack of a high quality simultaneous fetal electrocardiogram makes it impossible to perform end-diastolic measurements in accordance with the standards of the American Society of Echocardiography, which has recommended that end-diastole be considered the onset of the QRS complex. Diastolic ventricular measurements are usually made at the point of maximal chamber dimension, at the level of the mitral leaflets. Measurements are made, when possible,

0735-1097/85/$3.30

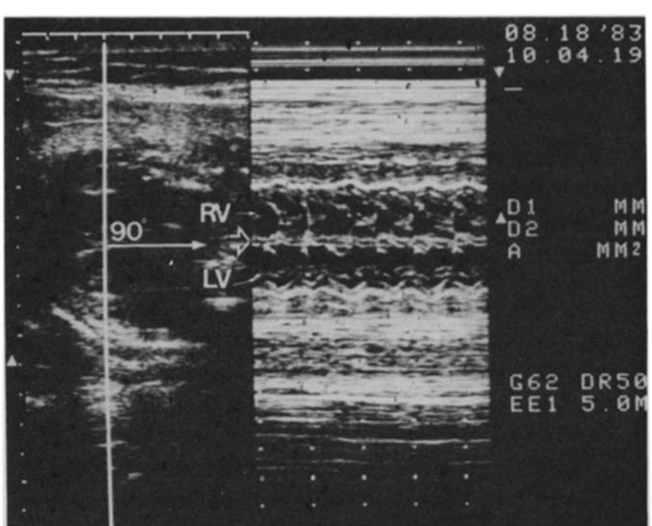
when the M-mode scan has been oriented utilizing the four chamber view of the fetal heart (Fig. 1).

Concept of "combined ventricular output." To describe cardiac output and regional organ blood flow in the fetal lamb, in which the ventricles function in parallel rather than in series, the concept of "combined ventricular output" has been developed (7). Rudolph and Heymann (8) demonstrated that the fetal lamb ejects approximately two-thirds of the combined ventricular output from the right ventricle. The one-third of combined output that is ejected from the left ventricle is distributed predominantly to the heart, brain, upper trunk and forelimbs. The disparity between right and left ventricular outputs is less marked in the human fetus, in which the brain receives a considerably higher percent ($\approx$15 to 20%) of the combined ventricular output than the approximately 3% it receives in the fetal lamb (9). In addition, change in the relative blood flow distributed to the brain of the human fetus during late gestation alters the relative right and left ventricular volumes over the course of development.

This relative "volume overload" of the fetal right ventricle may have an important influence on efforts to perform volumetric studies of the fetal heart.

Pre- versus postnatal ventricular shape. In 1972, Winsberg (10), using M-mode echocardiography, applied geometric formulas to convert left ventricular linear dimensions to ejection fraction, stroke volume and cardiac output determination in the human fetal heart. The formulas used were based on a geometric model assuming the left ventricle to resemble, as in the postnatal state, a prolate ellipse. Although this report represented the first effort to generate such data in the intact human fetus, these calculations may have been flawed by the assumption that the fetal left ventricle has the same shape that it will assume postnatally.

Figure 1. Simultaneously recorded two-dimensional and M-mode echocardiographic study in a 32 week old fetus. The M-mode scan is recorded at the level of the mitral valve. The M-mode "cursor" is perpendicular to the plane of the interventricular septum (**long arrow**). The right ventricular cavity (RV) (**small arrow**) dimension (15 mm) exceeds that of the left ventricle (LV) (**small arrow**) (12 mm) by a ratio of 1.2. The interventricular septal (**open arrow**) motion is flat.



We have noted (1) flattened or paradoxic interventricular septal motion in more than one-half of the fetal studies performed during the midportion of the third trimester. This observation has suggested that the right ventricle of the human fetus, like that the fetal lamb, is relatively volume "overloaded." This results in end-diastolic displacement of the interventricular septum into the left ventricle. The latter finding has been subsequently confirmed in our two-dimensional studies of fetal cardiac structure. This produces a relative "flattening" or "pancaking" of the left ventricular cavity. Azancot et al. (11), using short-axis two-dimensional fetal scans, noted the same "flattening" of left ventricular contour during diastole. They observed less distortion of the left ventricle immediately postnatally and even less in the 3 month old infant. All of these data suggest that the fetal human heart, like that of the fetal lamb, has a larger right to left ventricular volume ratio in utero than it does postnatally. In addition, geometric models of left ventricular shape that are of use in determining ventricular volumes postnatally may be inaccurate when applied to the fetus. Allan et al. (12) and Wladimiroff et al. (13,14), using M-mode echocardiography, demonstrated right and left ventricular transverse dimensions that are approximately equal between the 16th and 40th weeks of gestation. Although Allan et al. did not study these fetuses postnatally, the data of Wladimiroff et al. show an immediate alteration in the ratio of right to left ventricular dimension from 1.0 to 0.6 within 10 minutes of delivery. These data support the concept of relative right ventricular dilation in utero. Our data are in closer agreement with those of Sahn et al. (15), who found a prenatal right ventricular/left ventricular ratio of 1.18 ± 0.01 compared with 0.99 ± 0.03 within 36 hours of birth.

In the fetal heart, alterations in ventricular output may alter the relative sizes of the ventricular cavities. This may be associated with either structural or functional derangements. We encountered marked left ventricular dilation in an hydropic fetus who was subsequently diagnosed to have a left ventricular infarction (16). In contrast acute right ventricular dilation was encountered in two fetuses with "idiopathic fetal hydrops" and may be found in preterminal fetuses with severe intrauterine growth retardation and placental insufficiency (Fig. 2). The increased disparity in ventricular dimensions may result from an acutely increased afterload in the placental circulation. Increased impedance to right ventricular ejection results in acute right ventricular failure and dilation. This finding has a correlate using fetal

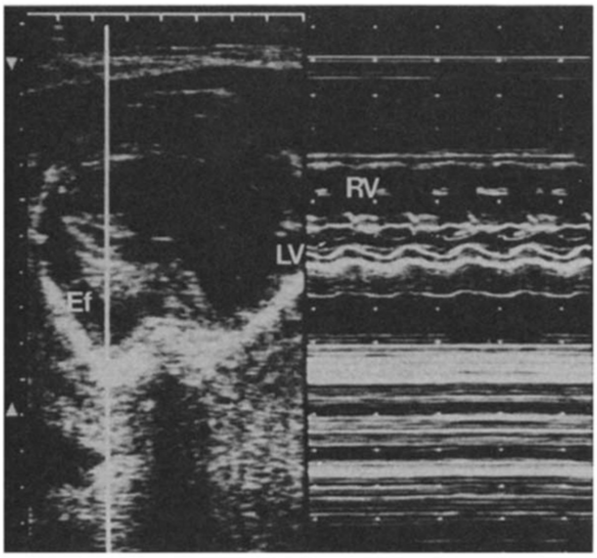


Figure 2. Simultaneously recorded two-dimensional and M-mode echocardiographic study in an hydropic, growth-retarded 32 week fetus. There is a large pleural effusion (Ef). The right ventricular (RV) cavity dimension (16 mm) exceeds that of the left ventricle (LV) (**arrow**) (9 mm) by a ratio of 1.8. Cardiac configuration was normal.

animal models, in which acutely increased afterload on the right ventricle, accomplished by inflation of a balloon in the descending aorta, produced a decrease in right ventricular output and fetal heart rate (8). This suggests that evaluation of right ventricular dimension and relative ventricular size may be used as a barometer of fetal circulatory function (Fig. 3). We are currently investigating the use of a two-dimensional model of the combined ventricular mass as a means of assessing fetal cardiac pump function. Our efforts have been hampered by the low sampling rates of current two-dimensional imaging equipment and the difficulties inherent in storing this information for later retrieval from video tape recorders, which are poorly suited for analysis of volume changes in the rapidly beating fetal heart.

Systolic Time Intervals

In recent years, perinatologists have attempted to assess the well-being of human fetuses through examination of fetal cardiac electromechanical time intervals using Doppler ultrasound (17). Cardiologists have used systolic time interval measurements computed from external pulse and phonocardiographic and electrocardiographic recordings (18) and, more recently, from M-mode echocardiographic recordings of semilunar valve opening and closure (19,20) as a noninvasive technique for the evaluation of systolic ventricular performance and vascular impedance. Simply stated, the systolic time intervals consist of the pre-ejection period and the ventricular ejection time. The pre-ejection period consists of the electromechanical delay (the onset of the QRS complex to the onset of ventricular contraction) and the isovolumic contraction period (the onset of ventricular contraction to semilunar valve opening). The ventricular ejection time is the period between semilunar valve opening to valve closure. The duration of these intervals depends on five factors: preload, afterload, contractile state of the myocardium and the rate and sequence of intraventricular electrical conduction.

We developed a technique for the measurement of systolic time intervals in the human fetal heart (21). Studies were performed on fetuses between 22 and 42 weeks' gestation, using M-mode echocardiographic recordings of fetal semilunar valves, and simultaneously inscribed fetal electrocardiographic signals that were obtained utilizing electrodes placed on the maternal abdominal wall. Because the electrocardiographic channels supplied with commercially available echocardiographs do not have sufficient gain to detect

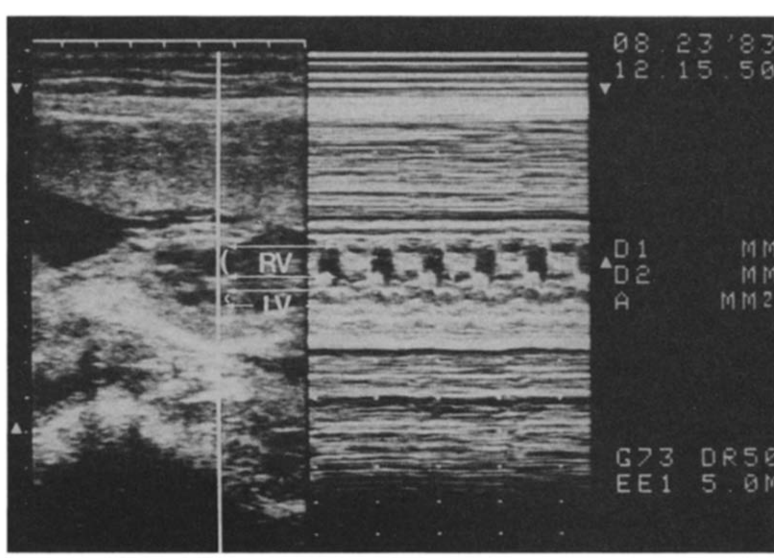


Figure 3. Simultaneously recorded two-dimensional and M-mode echocardiographic study in a 20 week old fetus. This fetus had massive right atrial enlargement, right ventricular (RV) dilation (11 mm), tricuspid valve dysplasia and pulmonary atresia. The right ventricular dimension exceeds that of the left ventricle (LV) (6 mm) by a ratio of 1.8. **Arrows** connect corresponding structures in two-dimensional and M-mode tracings.

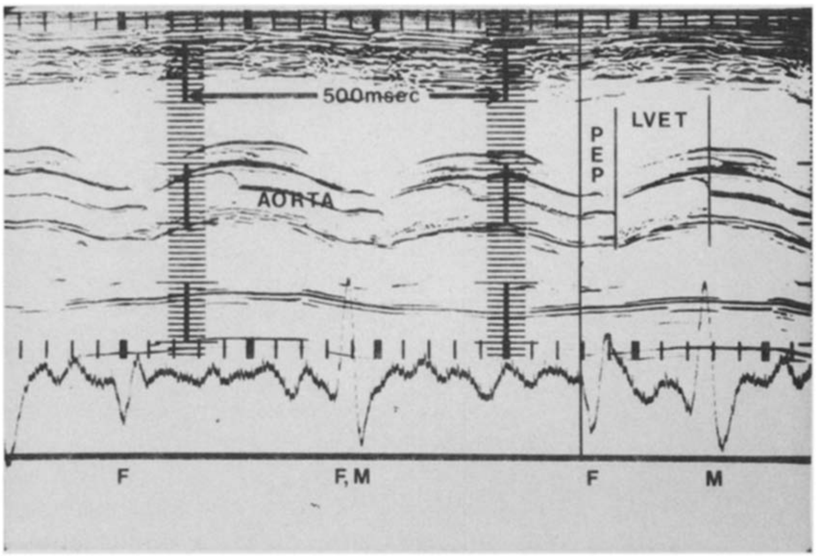


Figure 4. Left ventricular systolic time intervals measured from simultaneously inscribed M-mode echocardiogram of aortic valve motion and electrocardiogram showing maternal (M) and fetal (F) QRS complexes. The pre-ejection period (PEP) is measured from the onset of fetal electrical activation to aortic valve opening. The left ventricular ejection time (LVET) is measured from semilunar valve opening to closure.

the fetal signal, a preamplifier was used. The signal was processed through a low frequency filter.

The pre-ejection period was measured from the point of onset of the fetal QRS complex to the opening of the semilunar valves. The ejection times of the two ventricles were measured from the point of opening to the closure of their respective semilunar valves (Fig. 4). The ratio of pre-ejection period/ventricular ejection time was independent of heart rate, but was positively correlated with gestational age (Fig. 5A). The latter finding was due to a lengthening of pre-ejection period with a negligible change in ventricular ejection time. In studies of the fetal lamb, Organ et al. (22) observed a prolongation of pre-ejection period with cord occlusion. This was attributed to an acutely increased afterload and a decreased preload. Human fetal studies utilizing Doppler techniques have similarly shown prolongation of the pre-ejection period associated with cord compression.

Some studies have suggested that stressed and hypoxic fetuses may actually have a shortened pre-ejection period (23). This has been attributed to an enhanced inotropic state associated with a stress-related release of catecholamines. If this is true, it may be expected that further study will show a variable pre-ejection period response at varying gestational ages, depending, in part, on the level of development of sympathetic innervation. Animal studies (8) have demonstrated a great interspecies variation in the time of appearance of sympathetic innervation of the heart. In the lamb, innervation is present at 0.6 gestation and well developed at term (24). The level of development of sympathetic innervation in the human fetus is not certain, but developmental changes in the degree of innervation may be expected to alter cardiac responsiveness to stress at different gestational ages.

We have encountered a fetus at 27 weeks' gestation with hydrops fetalis, polycystic kidneys and no evidence of structural heart disease. There was marked right heart dilation with pericardial effusion. Markedly abnormal systolic time intervals were noted. The pre-ejection period was nearly twice the expected value (100 versus 55 ms), with a shortened left ventricular ejection time. The pre-ejection period/left ventricular ejection time ratio (0.9) was nearly three times the predicted value for this gestational age (0.22 to 0.35) (Fig. 5B). This finding is consistent with our hypothesis that nonimmune hydrops fetalis represents end-stage congestive heart failure in utero.

The use of M-mode echocardiography, with spatial orientation of the transducer beam utilizing a simultaneous or sequential two-dimensional scan, allows these measurements to be performed with correct identification of the semilunar valves involved (21). Although one might expect the ejection times of the two ventricles to be simlar because of the nonrestrictive ductus communication in utero, it has, in fact, been found that the ejection times of the two ventricles differ from one another. Nisand et al. (25) found the left ventricular ejection time to exceed the right ventricular ejection time. In four cases in which pulmonary and aortic valves were recorded simultaneously in our laboratory, right ventricular ejection time exceeded left ventricular ejection time (Fig. 6). These findings are compatible with a greater volume ejection from the right ventricle. Further study will be necessary to reconcile these disparate findings, which may be attributable to our small sample or may be a function of the earlier gestational ages in our sampling (as early as 22 weeks) compared with those in the study of Nisand et al. (32 to 42 weeks) and the alteration in relative ventricular volumes later in human gestation as brain flow increases.

Although while promising as a means of assessing pump function, fetal systolic time interval measurements are difficult to obtain, largely because of the low (50 to 60%)

JACC Vol. 5, No. 1
January 1985:84S–94S

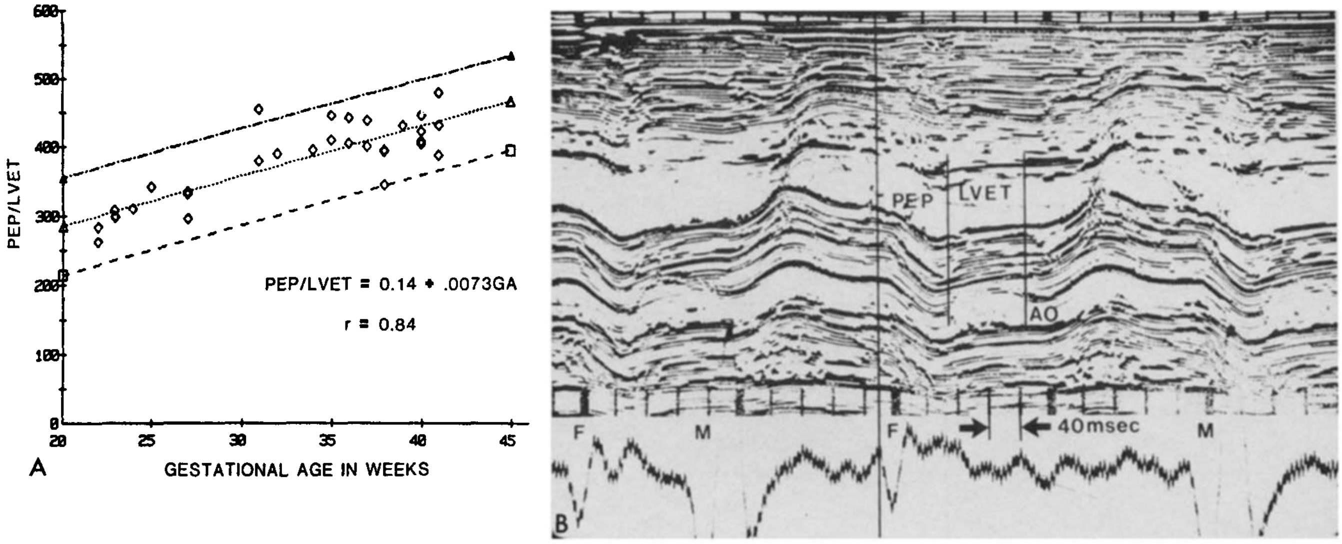


Figure 5. A, The ratio pre-ejection period/left ventricular ejection time (PEP/LVET) is independent of heart rate but directly correlated to gestational age. B, The PEP/LVET was grossly elevated (0.9) in a severely hydropic 27 week old fetus. ◇, data points; ▲, △, □, 95% confidence limits.

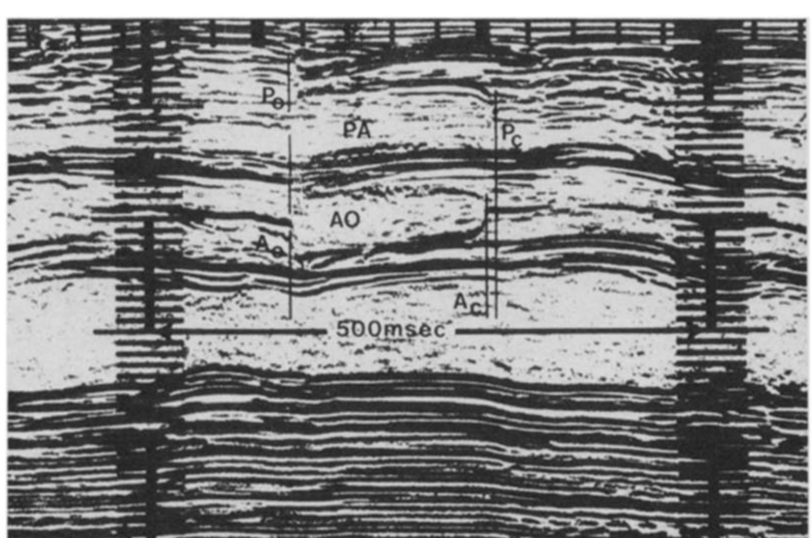
success rate in recording adequate transabdominal fetal electrocardiograms against the background interference from the maternal electrocardiograms.

Postextrasystolic Potentiation

We have investigated the ability of the human fetal heart to manifest postextrasystolic potentiation to determine whether the fetal heart can modulate its contractile state. Although previous animal studies have suggested that the fetal lamb heart exhibits postextrasystolic potentiation (26,27), it has been suggested that such potentiation is limited in the human neonate (28). Little evidence exists concerning whether this property exists in the human fetus (29).

We have analyzed M-mode echocardiographic tracings of human fetal hearts between 32 and 37 weeks' gestation in which spontaneously occurring isolated atrial or ventricular extrasystoles were documented. Measurements of right and left ventricular chamber size, shortening fraction and wall thickness were evaluated as was peak systolic wall velocity (the latter was measured because it is an index independent of "geometric assumptions" concerning ventricular shape) at baseline and during the first postextrasystolic beat. Our findings were compatible with the presence of postextrasystolic potentiation in the human fetus. Although we are unable to state whether this is due to increased preload, decreased afterload or enhanced contractility (perhaps calcium-mediated), it suggests that the human fetus can modulate its contractile state in a manner that is measurable using fetal echocardiography. Although this may

Figure 6. Simultaneously inscribed M-mode echocai diograms of pulmonary (PA) and aortic (AO) valve: Pulmonary and aortic valve opening (P_o and A_o, re spectively) were simultaneous, whereas pulmonar closure (P_c) occurred later than aortic closure (A_c).



have some potential for monitoring in utero antiarrhythmic therapy in a setting where spontaneous extrasystoles are common, these measurements are of limited practical use as a screening technique because of the rarity and unpredictable occurrence of spontaneous extrasystoles in the fetal heart. In addition, the site of origin (atrial versus ventricular, right-sided versus left-sided) of the extrasystoles could alter preload substantially and thereby influence the presence and degree of potentiation of ventricular contraction.

Doppler Flow Studies

The techniques described do not provide information concerning fetal cardiac flow. This information may be attainable using the newer techniques of pulsed and continuous wave Doppler flowmetry. The initial experience with these techniques is encouraging (30–32) because flow estimates have been both reproducible and quantitatively similar to the flows that have been reported (33,34) (descending aortic flow 185 to 261 $\text{ml·min}^{-1}\text{·kg}^{-1}$; umbilical venous flow 115 $\text{ml·min}^{-1}\text{·kg}^{-1}$) using other measurement techniques. The potential errors in Doppler measurement techniques are, however, substantial. These are easily explained by examining the standard form of the Doppler equation for quantifying flow:

$$V = \frac{f_D c}{2 f_o \cos\theta},$$

where V = velocity, f_D = output of the mean frequency demodulator; c = velocity of ultrasound in blood (1,570 m/s); cos = cosine; f_o = operating frequency and θ = angle between insonating beam and vessel. The blood flow (Q) is then calculated from V according to the equation:

$$Q = V\pi\left(\frac{d^2}{4}\right),$$

where d is the diameter of the vessel.

For any small error in measurement of the angle θ, the cos θ term will be altered very little for small angles ($\theta <$ 30°). If the insonating beam approaches the blood vessel being studied at an angle greater than 45 to 60°, however, a small error in measurement of θ will result in a large error in the cos θ term and, therefore, impart a large error in the calculation of velocity. In the active fetus it may be difficult to insure a consistent incident angle of less than 45°. In addition, any error in measurement of vessel diameter (d), either due to vessel pulsation, lack of clear definition of lumen boundary or tangential view of the vessel lumen, will again impart substantial error. In vitro tests in vessels ranging from 0.5 to 1.5 mm in diameter and insonating angles less than 45° have resulted in average accuracies of 85% in flow calculations (35). Further in vitro and in vivo experiments analyzing errors introduced by inaccurate vessel measurement suggest that such errors can be held below 10%. Hence, Doppler flow studies hold great promise for the analysis of umbilical and aortic flow. In the absence of quantitative flow estimates, Doppler waveform analysis may provide valuable information concerning directional flow within the heart and blood vessels and may detect valvular insufficiency, absent, decreased or reversed foramen ovale shunting and altered flow patterns associated with fetal arrhythmias.

Fetal Cardiac Rhythm

Disturbances of fetal cardiac rhythm are usually first suspected on the basis of auscultatory findings. Because of the inability of transabdominal electrocardiography to distinguish atrial depolarization, this technique is of limited value for the analysis of in utero cardiac arrhythmias. Utilizing M-mode recordings of cardiac motion against time, we have drawn (36) conclusions regarding electrical events in the fetal heart as they are reflected by the mechanical responses that are recorded echocardiographically. Our technique involves registration of M-mode tracings of atrioventricular valve motion, atrial and ventricular wall contraction sequence and interventricular septal motion. Scans are located on the fetal heart using a simultaneously inscribed two-dimensional image. These techniques provide a noninvasive means of diagnosing rhythm disturbances in the fetal human heart, and monitoring efforts at transplacental antiarrhythmic therapy (Fig. 7).

Supraventricular tachyarrhythmia. We have encountered 13 cases of sustained supraventricular tachyarrhythmia during the past 3 years. These have included nine cases of supraventricular tachycardia, three cases of atrial flutter and one case of atrial fibrillation. Ten of the 13 fetuses had associated hydrops fetalis. Utilizing the M-mode fetal echocardiogram, the tachycardia was documented. Ventricular anatomy and dilation were assessed and pericardial effusions were identified. Transplacental therapy through maternal administration of antiarrhythmic agents, including digoxin, verapamil, propranolol and procainamide, was monitored echocardiographically. With these agents alone or in combination, eight of the nine fetuses with supraventricular tachycardia were successfully treated transplacentally and delivered as normal healthy infants at term. The ninth fetus was delivered by cesarean section at 34 weeks' gestation after an unsuccessful effort at arrhythmia control with digoxin and propranolol therapy. The neonate eventually did well, but only after a harrowing neonatal period that involved respirator management of hyaline membrane disease, multiple thoracenteses and paracenteses for control of tense ascites and pleural effusions and multiple episodes of electrical cardioversion. Since that experience, we have employed verapamil in combination with digoxin for control of in utero supraventricular tachycardia in three patients.

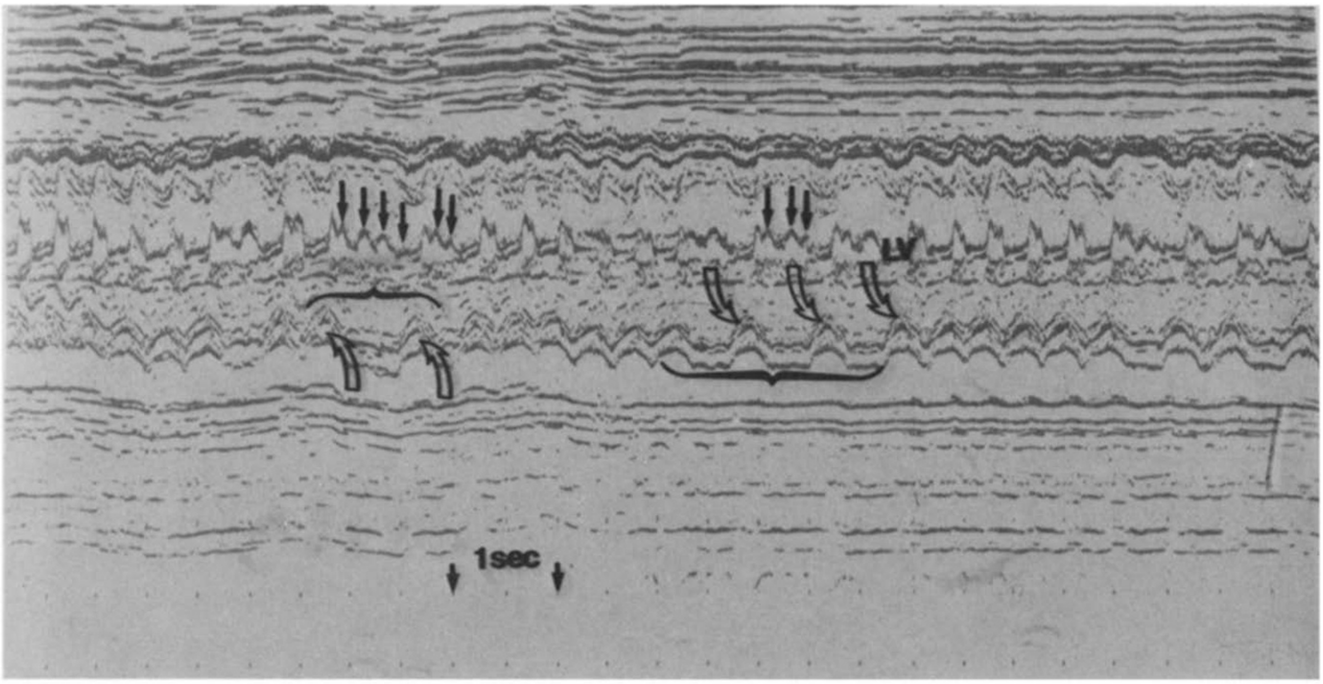


Figure 7. M-mode echocardiogram in a 32 week old fetus with supraventricular tachyarrhythmia. Motion of left ventricular (LV) posterior wall (**curved arrows**) suggests an irregular ventricular response caused by a variable atrioventricular block. Rapid undulations reflecting atrial flutter rate of 480 beats/min are reflected on the atrioventricular valves (**vertical arrows**). This echocardiogram was recorded after administration of digoxin and verapamil to the mother of the fetus.

The fetal echocardiogram was used to monitor the fetal response to therapy.

Bradycardia. The sudden onset of severe bradycardia secondary to complete or high grade second degree heart block may be associated with hydrops fetalis due to the sudden increase in ventricular diastolic dimension associated with the bradycardia. In the presence of the noncompliant fetal ventricle (24), the increased volume is associated with a marked increase in end-diastolic pressure. In such cases, we recommend consideration of early delivery and pacemaker management. Early in gestation, with pulmonary immaturity, we would focus efforts on increasing heart rate, possibly through the administration of beta-adrenergic agents to the mother (for example, isoproterenol or Ritodrine). Ritodrine, if associated with improved fetal status as demonstrated by decreased ventricular dimension and resolution of hydrops fetalis, could be chronically maintained in an oral form.

Isolated versus sustained arrhythmia. Our initial studies are consistent with those of other investigators (37) who have suggested that isolated ventricular or atrial extrasystoles are of little or no hemodynamic consequence and that most will spontaneously resolve later in pregnancy or during the first days of life. Follow-up study may be indicated, however, because of the possibility that an extrasystole may occur at a coupling interval that will incite a sustained reentrant tachycardia. We have experienced one such occurrence.

We have found that sustained arrhythmias, when associated with severe congenital cardiac malformations (tetralogy of Fallot in one case and an atrioventricular septal defect in another) have a poor prognosis, and both of these hydropic fetuses died in the neonatal period.

Limitations of echocardiography in diagnosing fetal arrhythmia. The use of the echocardiogram to delineate electrical events in the fetal heart is not without its difficulties. We recently encountered in a diabetic mother a fetus with evidence of hypertrophic cardiomyopathy and protracted episodes of sustained tachycardia at approximately 200 beats/min. During episodes of sustained tachycardia, the fetus developed gasping respirations at a rate of 80 to 100 breaths/min. This was interpreted as evidence of fetal distress (38). Amniocentesis was performed, demonstrating evidence of inadequate pulmonary surfactant production. Efforts were made to "treat" the arrhythmia with transplacentally administered digoxin. This was maintained throughout the last 6 weeks of pregnancy with in-patient echocardiographic monitoring of cardiac size, rhythm and respiratory pattern. The gasping resolved and the frequency of episodes of tachycardia diminished. Soon after birth of a well infant with hypertrophic cardiomyopathy, this child developed sustained ventricular tachycardia at approximately 160 beats/min. This arrhythmia was associated with retrograde atrial activation. During the tachycardia, echocardiograms showed a regular relation between atrial and ventricular activity, demonstrating the weakness of echocardiography for distinguishing ventricular tachycardia without atrioventricular dissociation from supraventricular tachycardia. Although this newborn infant did quite well on quinidine therapy, potential harm could have resulted from the digitalis administration, showing the need for close continued monitoring of these patients and also demonstrating that administration of these medications in the absence of clear-cut evidence of fetal congestive heart failure may not be justifiable using a risk/benefit analysis.

Hypertrophic Cardiomyopathy in the Infant of the Diabetic Mother

The diabetic pregnancy represents a unique situation. These fetuses are at risk for hypertrophic cardiomyopathy, thought to be secondary to the chronic fetal hyperinsulinemia mounted in response to chronic maternal hyperglycemia (39). This hypertrophic myopathy, which is usually found in association with gross fetal macrosomia, may place the neonate in jeopardy, as a result of either dynamic ventricular outflow tract obstruction or severe restriction to ventricular filling. This myopathy has been encountered in a stillborn second trimester fetus and has also been diagnosed echocardiographically during the midportion of the second and during the third trimesters of pregnancy. Experience with neonates with this cardiomyopathy has demonstrated that children who survive the neonatal period will gradually recover, with spontaneous resolution of the condition.

Our experience with fetuses with hypertropic myopathy in utero has been limited to three cases (Fig. 8). One of these cases was encountered during the second trimester in a fetus whose mother's diabetes was poorly controlled. The myopathy gradually improved as diabetic control improved later in gestation. Free wall and interventricular septal thickness actually diminished during later gestation and were within normal range by the time of birth. A survey of 50 women with diabetes enrolled in our high risk obstetric clinic showed no difference in fetal cardiac dimensions or wall thicknesses when compared with control fetuses at similar gestational ages and estimated fetal weights (40). It has been suggested (41), and our clinical experience supports this hypothesis, that fetal macrosomia and hypertrophic myopathy are a function of the adequacy of blood sugar control of the diabetic mother rather than representing a function of duration of the diabetic state before pregnancy. Therefore, we have looked on fetal echocardiographic evalution of cardiac structure in fetuses of diabetic mothers as a means not only of detecting possible structural heart disease in the fetus, but also as a means of assessing the adequacy of diabetic control.

Limitation of fetal studies. We have been successful in obtaining fetal cardiac images in 95% of cases studied between 18 and 40 weeks' gestation in nondiabetic mothers. Our higher failure rate with diabetic mothers has been accounted for primarily by difficulties inherent to studies attempted on obese mothers, in whom the fetal heart is so far

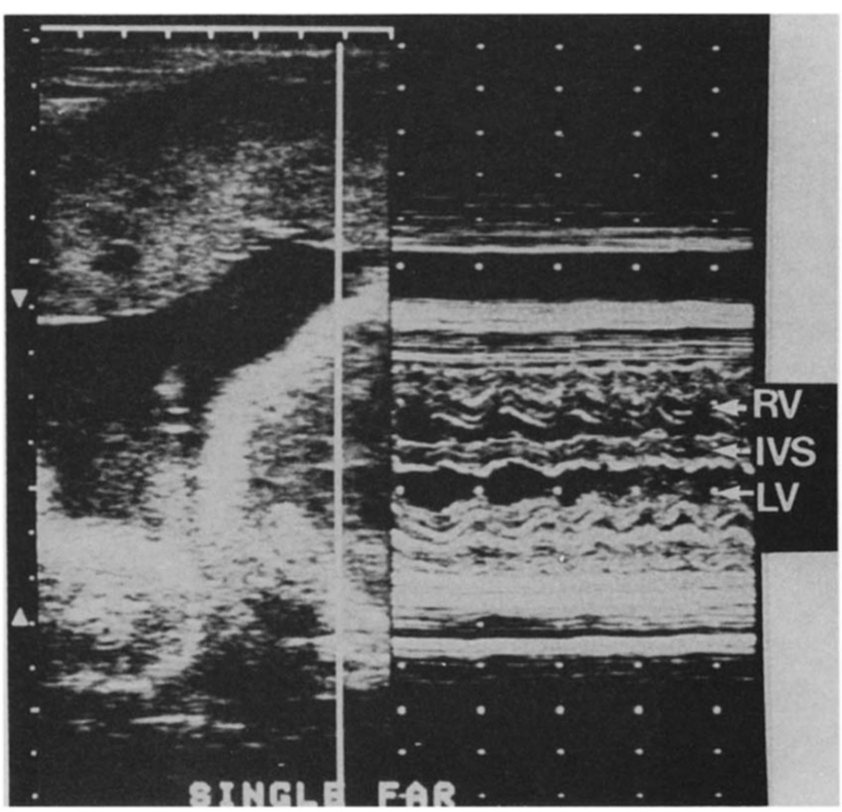


Figure 8. Simultaneously recorded two-dimensional and M-mode echocardiographic study in a 32 week old fetus of a diabetic mother. The thickness of the interventricular septum (IVS) (7 mm) is consistent with hypertrophic cardiomyopathy. LV = left ventricle; RV = right ventricle.

JACC Vol. 5, No. 1
January 1985:84S–94S

from the maternal abdominal wall that lower frequency (2.25 MHz) ultrasound is required to attain adequate tissue penetration (we prefer to use 3.0 to 5.0 MHz sources). At the lower frequency range, spatial resolution may be too poor to allow adequate fetal cardiac study. Unfortunately, maternal obesity is frequently encountered in diabetic mothers, resulting in a much higher (30 to 40%) failure rate of study in this group.

Nonimmune Hydrops Fetalis

Fetal echocardiographic studies in fetuses with nonimmune hydrops have given information that may be put to practical use in the management of these offspring. With the declining frequency of Rh isoimmunization in the western world, nonimmune hydrops fetalis has become the predominant form of hydrops encountered by perinatologists. Previous reports (42) have indicated that mortality rates from this condition approximate 100%. The contribution of nonimmune hydrops to total perinatal mortality has increased over a 10 year period from 0.1 to 3% (43). Although a large number of fetal abnormalities may result in hydrops fetalis, we and, more recently, others (16) have noted a large proportion of cases of nonimmune hydrops to have an identifiable cardiovascular explanation for "heart failure" and resulting systemic edema. The fetal echocardiogram has been useful in identifying these causes of circulatory decompensation.

Pathophysiology. The underlying pathophysiologic mechanism appears to be related to acute volume or pressure overload, or both, of the fetal right atrium with subsequent development of systemic venous hypertension. Due to the parallel flow cicuits within the fetal heart and the communication at the level of the foramen ovale, acute alterations in the filling characteristics of either fetal ventricle will cause an alteration in right atrial emptying. Data from the study of fetal lamb hearts suggest decreased compliance in the fetal ventricle compared with neonatal and adult ventricles due to a relative paucity of contractile elements in the fetal myocardium. There is also a more marked influence in utero of diastolic hypertension in one ventricle on the filling characteristics of the contralateral ventricle (24). For these reasons, a variety of cardiac malformations, including those associated with semilunar valve or atrioventricular valve regurgitation, functional abnormalities (myocarditis), mass lesions or sustained tachyarrhythmias may result in systemic venous hypertension and systemic edema. We noted severe hypoalbuminemia (< 1 g/dl) in two hydropic neonates with cardiac causes of hydrops (one with supraventricular tachycardia, one with an embolic left ventricular infarction). We believe that the hypoalbuminemia is due either to hepatic dysfunction secondary to severe systemic venous hypertension or to loss of albumin through the intestine, lungs or into third-spaced fluid. We have found pericardial effusions in 12 of the first 13 hydropic fetuses scanned and now consider pericardial effusion, especially in the presence of a sustained arrhythmia or ventricular chamber dilation, to be a harbinger of hydrops fetalis (44).

Role of early identification. We believe that it is important to identify specific causes of hydrops fetalis as early as possible during gestation in an effort to identify cases that could potentially be treated in utero. In a recent review of hydrops, Hutchison et al. (45) stated that the most consistent sequela of hydrops, occurring in more than 90% of cases, was pulmonary hypoplasia, presumably related to compression of the developing lung tissue by pleural effusions. This potentially fatal complication may be avoided if reversible causes of hydrops fetalis are identified and treated in utero and if, in selected cases, the child is delivered early, before the development of large pleural effusions. We, therefore, have advocated the use of fetal echocardiography as an adjunct to the obstetric ultrasound examination in evaluating the fetus with nonimmune hydrops. Because the condition of some hydropic fetuses rapidly worsens to an irreversible state, we recommend the expeditious ultrasonic evaluation of all pregnant women presenting with polyhydramnios (found in 74% of mothers with hydropic fetuses), pre-eclampsia (34% of mothers with hydropic fetuses) or a sudden decrease in fetal activity.

Conclusion

The grossly hydropic fetus represents the most serious manifestation of disordered pump function. The finding of disproportionate ventricular enlargement, pericardial effusion in the absence of generalized edema and other serous effusions, abnormal ventricular systolic time interval measurements, cardiac arrhythmias heralding the onset of sustained tachyarrhythmia (for example, frequent extrasystoles associated with short episodes of nonsustained supraven-

Table 1. Indications for Fetal Echocardiography

Fetal factors
Intrauterine growth retardation
Fetal cardiac arrhythmia
Fetal somatic anomalies (ultrasound)
Hydrops fetalis
Abnormal genetic screen
Decreased fetal movement
Maternal factors
Congenital heart disease
Polyhydramnios
Rh sensitization
Diabetes mellitus
Collagen vascular disease
Drug exposure (alcohol, anticonvulsants, lithium, etc.)
Pre-eclampsia
Familial factors
Congenital heart disease
Genetic syndromes

tricular tachycardia) or complete heart block (for example, second degree atrioventricular block in a fetus whose mother has systemic lupus erythematosus) are alarming and should be viewed as harbingers of more disordered circulatory function. If these signs are scrupulously sought, the sensitivity of fetal echocardiographic analysis for detecting functional disorders of the fetal circulatory system will be further improved.

These studies can be performed using commercially available echocardiographic equipment. Each examination requires approximately 30 to 40 minutes for completion. Unfortunately, it would be a prodigious and cost-ineffective undertaking to recommend routine ultrasound examination of every pregnant woman, although this approach is being made in some European centers. Despite the absence of any hard data to suggest the detrimental effect of ultrasound at these frequencies and energy levels either on the mother or offspring, we maintain that discretion dictates reserving such study for women whose fetuses are "at risk" for structural or functional heart disease (Table 1).

Fetal cardiac ultrasound studies have increased our understanding of normal and abnormal cardiac development in the human fetus. As a means of detecting abnormalities in cardiac structure and function and by providing a technique for monitoring our efforts at in utero treatment, the fetal echocardiogram has provided the cornerstone for the development of the first fetal cardiac diagnosis and treatment programs.

We thank Norman S. Talner, MD and John C. Hobbins, MD for encouragement and support, Diana C. Lynch, RN for technical expertise and Mary Beth Graham for secretarial skills.

References

1. Kleinman CS, Hobbins JC, Jaffe CC, Lynch DC, Talner NS. Echocardiographic studies of the human fetus: prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. Pediatrics 1980;65:1059–67.
2. Kleinman CS. Fetal echocardiography. In: Sanders, RC, ed. Ultrasound Annual 1982. New York: Raven, 1982:321–46.
3. Allan LD, Tynan MJ, Campbell S, et al. Echocardiographic and anatomical correlates in the fetus. Br Heart J 1980;44:444–51.
4. Allan LD, Tynan MJ, Campbell S, Anderson RH. Identification of congenital cardiac malformations by echocardiography in midtrimester fetus. Br Heart J 1981;46:358–62.
5. Brutsaert DL, Paulus WJ. Loading and performance of the heart as muscle and pump. Cardiovasc Res 1977;11:1–16.
6. DeVore GR, Donnerstein RL, Kleinman CS, Platt LD, Hobbins JC. Fetal echocardiography. I. Normal anatomy as determined by real-time-directed M-mode ultrasound. Am J Obstet Gynecol 1982;144:249–60.
7. Dawes GS. The foetal circulation. In: Foetal and Neonatal Physiology. Chicago: Year Book Medical, 1968:91–105.
8. Rudolph AM, Heymann MA. Fetal and neonatal circulation and respiration. Am Rev Physiol 1974;19:187–207.
9. Lind J. Human fetal and neonatal circulation. Some structural and functional aspects. Eur J Cardiol 1977;5:265–81.
10. Winsberg F. Echocardiography of the fetal and newborn heart. Invest Radiol 1972;7:152–8.
11. Azancot A, Caudell T, Horowitz S, et al. Quantitative two-dimensional echocardiographic studies of left ventricular shape in the normal fetus and newborn infant. In: Dellenbach P, ed. 1er Symposium International d'Echocardiologie Foetale. Strasbourg: Milupa Dietetique, 1982:150–4.
12. Allan LD, Joseph MC, Boyd EGCA, Campbell S, Tynan M. M-mode echocardiography in the developing human fetus. Br Heart J 1982;47:573–83.
13. Wladimiroff JW, McGhie J. Ultrasonic assessment of cardiovascular geometry and function in the human fetus. Br J Obstet Gynaecol 1981;88:870–5.
14. Wladimiroff JW, Vosters R, McGhie JS. Normal cardiac ventricular function during the last trimester of pregnancy and early neonatal period. Br J Obstet Gynaecol 1982;89:839–844.
15. Sahn DJ, Lange LW, Allen HD, et al. Quantitative real-time cross-sectional echocardiography in the developing normal human fetus and newborn. Circulation 1980;62:588–603.
16. Kleinman CS, Donnerstein RL DeVore GR, et al. Fetal echocardiography for evaluation of in utero congestive heart failure: A technique for study of nonimmune fetal hydrops. N Engl Med 1982;306:568–75.
17. Murata Y, Martin CB Jr. Systolic time intervals of the fetal cardiac cycle. Obstet Gynecol 1974;44:224–32.
18. Weissler AM, Harris WS, Schoenfeld CD. Bedside technics for the evaluation of ventricular function in man. Am J Cardiol 1969;23:577–83.
19. Gutgesell HP, Paquet M, Desmond FD, McNamara DG. Evaluation of left ventricular size and function by echocardiography: results in normal children. Circulation 1977;56:457–62.
20. Hirschfeld S, Meyer R, Schwartz DC, Korfhagen J, Kaplan S. Measurement of right and left ventricular systolic time intervals by echocardiography. Circulation 1975;51:304–9.
21. DeVore GR, Donnerstein RL, Kleinman CS, Hobbins JC. Real-time-directed M-mode echocardiography: a new technique for accurate and rapid quantitation of the fetal preejection period and ventricular ejection time of the right and left ventricles. Am J Obstet 1981;141:470–71.
22. Organ LW, Bernstein A, Hawrylyshyn PA. The pre-ejection period as an antepartum indicator of fetal well-being. Am J Obstet Gynecol 1980;137:810–819.
23. Organ LW, Bernstein A, Smith KC, Rowe IH. The pre-ejection period of the fetal heart: patterns of change during labor. Am J Obstet Gynecol 1974;120:49–55.
24. Friedman WF. The intrinsic physiologic properties of the developing heart. In: Friedman WF, Lesch M and Sonnenblick EH, eds. Neonatal Heart Disease. New York: Grune and Stratton, 1973:1–32.
25. Nisand I, DeGeeter B, Rassier F, Spielmann A, Dellenbach P. Systolic time intervals in the human fetus. In Ref 11:186–96.
26. Kirkpatrick SE, Naliboff J, Pitlick PT, Friedman WF. Influence of poststimulation potentiation and heart rate on the fetal lamb heart. Am J Physiol 1975;229:318–23.
27. Anderson PAW, Manring A, Crenshaw C Jr. Biophysics of the developing heart. I. The force-interval relationship. Am J Obstet Gynecol 1980;138:33–43.
28. Arcilla RA, Lind J, Zetterquist P, Oh W, Gessner IH. Hemodynamic features of extrasystoles in newborn and older infants. Am J Cardiol 1966;18:191–9.
29. Rihl J. Zur erklärung der vergrösserung der postextrasystolischen systole des säugethierherzens. Z Exp Pathol Therapie 1906;3:1–18.
30. Eik-Nes SH, Brubakk AO, Ulstein MK. Measurement of human fetal blood flow. Br Med J 1980;280:283–4.
31. Eik-Nes SH, Marsal K, Brubakk AO, Kristofferson K, Ulstein M. Ultrasonic measurement of human fetal blood flow. J Biomed Eng 1982;4:28–36.

JACC Vol. 5, No. 1
January 1985:84S–94S

32. Kurjak A, Rajhvajn B Jr. Ultrasonic measurements of umbilical blood flow in normal and complicated pregnancies. J Perinat Med 1982;10:3–16.

33. McCallum WD. Thermodilution measurement of human umbilical blood flow at delivery. Am J Obstet Gynecol 1977;127:491–6.

34. Assali NS, Racsramo L, Peltonen T. Measurement of uterine blood flow and uterine metabolism. Am J Obstet Gynecol 1960;79:86–98.

35. Kosoff J. New clinical applications. In: Kurjak A, ed. Progress in Medical Ultrasound. I. Amsterdam: Excerpta Medica, 1980:27–42.

36. Kleinman CS, Donnerstein RL, Jaffe CC, et al. Fetal echocardiography. A tool for evaluation of in utero cardiac arrhythmias and monitoring of in utero therapy: analysis of 71 patients. Am J Cardiol 1983;51:237–43.

37. Southall DP, Richards J, Hardwick RA, et al. Prospective study of fetal heart rate and rhythm patterns. Arch Dis Child 1980;55:506–11.

38. Patrick J. Fetal breathing movements. Clin Obstet Gynecol 1982;25:787–803.

39. Breitweser JA, Meyer RA, Sperling MA, Tsang RC, Kaplan S. Cardiac septal hypertrophy in hyperinsulinemic infants. J Pediatr 1980;96:535–9.

40. Talner NS, Kleinman CS, Donnerstein RL, DeVore GR, Hobbins JC. The echocardiographic evaluation of fetal cardiac structure. In Ref 11:110–7.

41. Mace S, Hirschfeld SS, Riggs T, et al. Echocardiographic abnormalities in infants of diabetic mothers. J Pediatr 1979;95:1013–9.

42. Beischer NA, Fortune DW, Macafee J. Nonimmunological hydrops fetalis and congenital abnormalities. Obstet Gynecol 1971;38:86–95.

43. Andersen HM, Hutchison AA, Fortune DW. Non-immune hydrops fetalis: changing contribution to perinatal mortality. Br J Obstet Gynaecol 1983;90:636–9.

44. DeVore GR, Donnerstein RL, Kleinman CS, Platt LD, Hobbins JC. Fetal echocardiography. II. The diagnosis and significance of a pericardial effusion in the fetus using real-time-directed M-mode ultrasound. Am J Obstet Gynecol 1982;144:693–700.

45. Hutchison AA, Drew JH, Yu VYH, et al. Nonimmunologic hydrops fetalis: a review of 61 cases. Obstet Gynecol 1982;59:347–52.